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Nosocomial Vaccinia Infection

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Although hospital-associated spread of vaccinia has been reported in the past, there have been no recent reports. This paper describes hospital-associated spread of vaccinia virus infection, supplies data on the environmental survival of vaccinia virus and offers recommendations for the management of patients with vaccinia that may minimize the hazard of infection in other high-risk patients.

THE WORLDWIDE INCIDENCE of smallpox has declined as the World Health Organization eradication program has progressed.[1] In the United States there has been a decrease in the number of yearly smallpox vaccinations and a subsequent decline in vaccination complications. Because of the decreasing threat of smallpox importation[2] the recommended policy of the United States Public Health Service (USPHS) is selective rather than universal vaccination.[3] However, with 6.7 million vaccinations carried out yearly as of 1973,[1] complications of vaccination are still being seen in clinical practice.

Hospital spread of vaccinia is a rare[4-9] but important complication. It is recognized as a possible hazard to inpatients in the current USPHS recommendation[3] and hospital infection control programs. However, there have been no reports in the English language literature documenting this danger in the last ten years.

Reports of Cases

PATIENT 1.—On May 3, 1975 a 19-year-old man, a native of India with a lifelong history of atopic dermatitis, was admitted with the diagnosis of disseminated vaccinia to a dermatology ward and placed in isolation requiring the use of gown and gloves. Although the patient had tolerated a smallpox vaccination without sequelae in 1963, revaccination ten days before this admission resulted in the eruption of hemorrhagic vesicles and umbilicated pustules over the face, neck, arms and thighs. He received 35 ml of vaccinia immune globulin (VIG) in divided doses, and was started on a course of oral erythromycin. Following this therapy the skin lesions crusted and formed scabs. Mild conjunctivitis was treated with topical administration of idoxuridine. On May 8, it was noted that 80 to 90 percent of the vaccinial scabs were gone. Later that day, three hours before discharge, the patient was released from isolation and was seen walking through the corridors of the ward in street clothes.

PATIENT 2.—On April 9, 1975, a 63-year-old woman who had been vaccinated at age 5 and with a history of mycosis fungoides was admitted to the hospital for electron beam therapy. Although the patient was not being treated with chemotherapy at that time, during the previous three years she had been treated with prednisone, Grenz (superficial, poorly-penetrating) ray therapy, methotrexate and topically administered nitrogen mustard. There was diffuse involvement with this cutaneous lymphoma, including bilateral axillary and inguinal lymphadenopathy and circulating Sézary cells. After a left inguinal lymph

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node biopsy study was carried out, the results of which confirmed the presence of mycosis fungoides, an abscess developed at the incision site leading to staphylococcal and streptococcal septicemia which was treated with parenteral antibiotics. On May 8, Patient 2 was seen in the same hallway where Patient 1 had been walking that afternoon.

On May 18, after four weeks of antibiotic therapy, Patient 2 again became febrile. Administration of antibiotics was discontinued two days later. On May 20, a massive eruption of 2 to 3 mm, nonpruritic, nontender macules occurred, which evolved into white pustules scattered over the trunk, hands and eyelids. In the intertriginous areas under the breast and in the perineum, the lesions were confluent. The patient noted no systemic and local symptoms. The leukocyte count was found to be 2,700 per cu mm. In the days that followed, many of the pustules umbilicated. Findings on multiple Gram stains, potassium hydroxide preparations, and bacterial and fungal cultures from the lesions were negative. Results of a biopsy study of one of the lesions were considered consistent with viral disease because of the presence of multinucleated giant cells and polymorphonuclear leukocytes in the upper and middermis, and the absence of fungi and bacteria, on periodic acid-Schiff (PAS) and Gram stains.

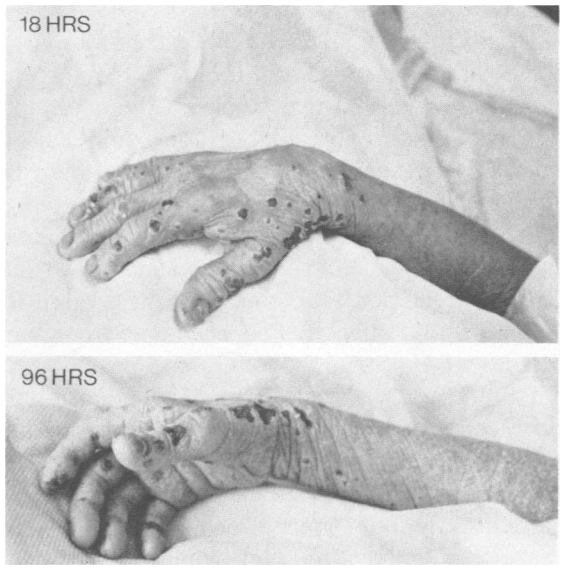

Figure 1.—Upper, vaccinia lesions of the hand 18 hours after administration of vaccinia immune globulin (VIG); **Lower,** 96 hours after VIG.

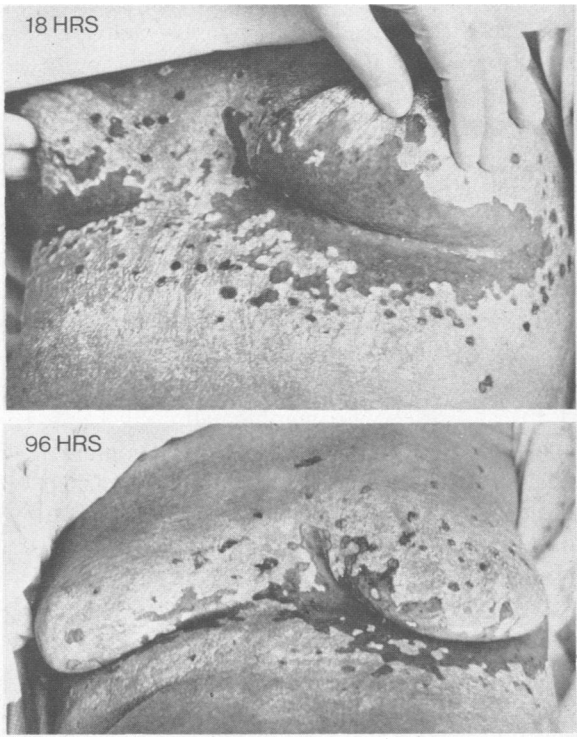

Figure 2.—Upper, vaccinia lesions of the intertriginous areas of the breasts 18 hours after administration of VIG; **Lower,** 96 hours after VIG.

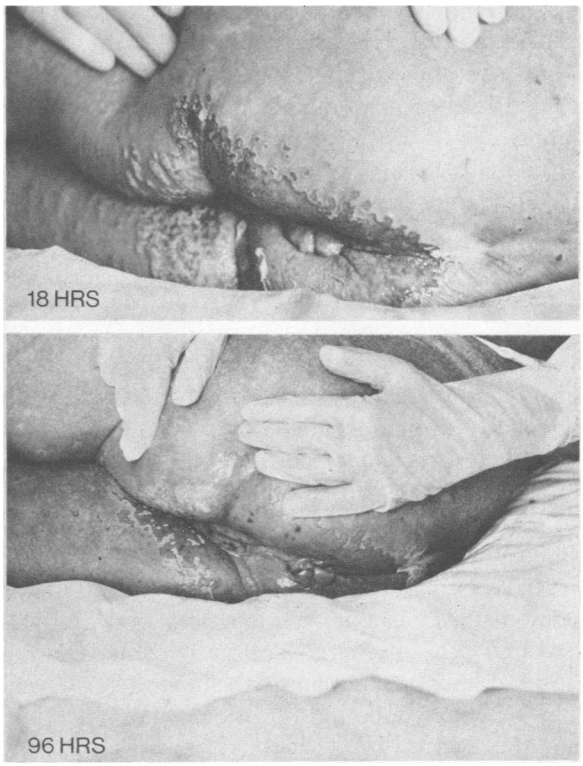

Figure 3.—Upper, vaccinia lesions of the perineum 18 hours after administration of VIG; **Lower,** 96 hours after VIG. Note the loss at 96 hours of edema of the borders of confluent lesions easily seen at 18 hours after VIG.

Fluorescent antibody (FA) tests of lesion scrapings were negative for herpes simplex and varicella-zoster viruses, but positive for vaccinia virus. Subsequently, tissue culture cells (infant foreskin fibroblasts) inoculated with vesicle fluid grew out vaccinia virus identified by a direct FA test. The indirect fluorescent vaccinia antibody titer was 1:256.

Subsequently, 0.6 ml per kg of body weight (32 ml) of vaccinia immune globulin was administered in divided doses. Significant crusting of the lesions was seen within 18 hours (Figures 1-3, upper) and further resolution was seen at 96 hours (Figures 1-3, lower). Because of the patient's presumed altered-immune, high-risk status, an additional 16 ml of vaccinia immune globulin was administered. After seven months, Patient 2 remains free of evidence of vaccinia virus infection.

Epidemiology

Patients 1 and 2 were seen in the same hallway at different times on May 8; their respective rooms were 75 feet apart. The isolation rooms in the hospital have double doors and are vented to the outside. The six-bed room that patient 2 shared with three other patients before isolation was not vented to the outside. Patients 1 and 2 never shared skin creams, blood pressure cuffs or other fomites.

In the case of Patient 2, a course of electron beam therapy and whirlpool therapy had been completed on May 17. On May 19 an x-ray study of the chest had been made and the patient was placed in a private room. Between May 18 and May 23 she was febrile and new skin lesions developed, but she was not put in isolation. On May 23, when the fluorescent antibody test was positive for vaccinia, Patient 2 was isolated with glove, mask, cap and gown precautions, and the entire ward was closed to new admissions. Two of Patient 2's previous roommates were immunosuppressed patients; they were placed in separate single rooms and vaccinia immune globulin was administered. The third roommate had psoriasis and had been discharged; she was recalled to the hospital and vaccinia immune globulin was given. The Hubbard tank and tub room, the x-ray room and the electron beam therapy rooms were decontaminated with Chlorox® (5.25 percent sodium hypochlorite) solution (1:20).

There were 106 people identified as possible contacts of one or both patients. These contacts were distributed among various hospital personnel groups. The husband and roommates of Patient 2 before her isolation were also included. Of 106 possible contacts, 31 were initially found on brief interview to have been at close contact with either Patient 2 alone (19/31) or both Patient 2 and Patient 1 (12/31).

Of the close contacts, 30 were interviewed in detail with a questionnaire. In all 30, blood specimens were taken on two occasions in June, separated by two to three weeks; no viral culture studies were attempted. No fever or skin rash developed in any of the 30 persons after contact with these patients. All had been vaccinated against smallpox in the past and nearly all had visible vaccination scars, but none who cared for Patient 1 or Patient 2 had been recently vaccinated.

Paired sera were selected from among the 30 close contacts on the basis of established contact with both patients. The sera were from seven nurses, one nursing assistant and two physicians. Paired sera were examined for evidence of significant rise in antivaccinia titer by means of complement fixation (CF),[10] hemagglutination inhibition (HI),[11,12] viral neutralization[13] and radioimmunoassay[14] tests. The results were unremarkable for HI and CF tests. Both members of each pair were positive with the radioimmunoassay and the neutralization tests. These results do not suggest recent infection but are consistent with previous vaccination.

Because of the possibility of transmission of vaccinia virus by means of environmental fomites, including hospital walls, and because there are no data in the literature on the environmental survival of vaccinia virus, studies were done to evaluate the possibility of environmental transmission of vaccinia.

Using a 19-gauge hypodermic needle, four drops of a dried calf-lymph smallpox vaccine, reconstituted and previously titered to contain $10^{6.9}$ pock-forming units per 0.1 ml, were placed on each of ten cleaned glass slides. The slides were dried and left in a decontaminated hood at a temperature of approximately 75°F (25°C).

The dried vaccine material on each slide was reconstituted with four drops of sterile, distilled water, using a 19-gauge hypodermic needle. A drop of the reconstituted material on each slide was inoculated onto each of the two chick chorioallantoic membranes (CAM) to quantitate the surviving virus. The results (Table 1) indicate

TABLE 1.—*Survival of Vaccinia Virus in a Reconstituted Smallpox Vaccine, After It Was Placed on Slides, Dried and Left at Room Temperature (About 25°C or 75°F)*

Hours Left at Room Temperature	Growth on Chorioallantoic Membrane*
0	Confluent
2	Confluent
4	Confluent
6	Confluent
10	Confluent
27	Confluent
30	Confluent
52	Confluent
78	Semiconfluent
144	Negative

*Inoculum = 1 drop through a 19-gauge hypodermic needle.

that vaccinia virus dried at room temperature and left at room temperature in a normal room environment was viable in large enough numbers at 78 hours that a drop of suspension gave semiconfluent growth on the CAM. However, no live virus titer was detectable at 144 hours. A noticeable decrease in live virus titer apparently began after 52 hours.

Discussion

It has generally been assumed that epidemiologic and other features of smallpox[15] apply to vaccinia. Currently there is insufficient information to confirm or negate the validity of this assumption.

Environmental Survival and Potential Transmission of Vaccinia Virus

Hospitals have been a frequent site for outbreaks of smallpox.[15] There have been several sporadic reports of vaccinia virus transmission within a hospital (for examples, see references 4-9). Five of the six cited epidemics were in dermatologic infirmaries or wards.[4-6,8,9] Findings in four of these reports were confirmed by modern virologic studies[6-9] and in two were suspected on clinical grounds.[4,5]

The spread of vaccinia virus infection is generally believed to require person-to-person contact[9,16] and has been seen in familial settings.[16,17]

The transmission of infectious vaccinia virus by fomites has not been shown to occur. However, Koplan and Marton[18] were able to culture virus from vaccinia scabs and from scab sites after the scabs had fallen off. Smallpox virus has been recovered from bedclothes, pillow swabs and back swabs of smallpox patients.[19] The results of this study show that infectious vaccinia virus in the absence of scabs may persist in the environment for three to four days. Whether vaccinia virus infection can be transmitted this way is presently unknown but our data suggest this possibility.

Epidemiologic Evaluation of the Transmission of Vaccinia from Patient 1 to Patient 2

The clinical diagnosis of vaccinia virus infection may be extremely difficult in the absence of a suggestive history, as the differential diagnosis of nonbacterial pustular dermatoses involves many different etiologic possibilities.[20] The diagnosis of vaccinia virus infection in Patient 2 was complicated by the initial absence of a suggestive history, and obscured by the underlying cutaneous lymphoma in this patient. However, when the clinical diagnosis of vaccinia was considered, it was rapidly confirmed by the fluorescent antibody test of vesicle scrapings, and the virus was grown in tissue culture subsequently. Therapy with vaccinia immune globulin was promptly initiated and such therapy may have been lifesaving. It is well-recognized that infection is the most common cause of death in patients with mycosis fungoides.[21]

Others at risk of acquiring clinically significant vaccinia infection include those with eczema or other chronic dermatoses, those with an acquired or inherited immune deficiency state, fetuses of pregnant patients and children younger than 12 months of age.[1]

The serologic data of the contact persons failed to show any recent vaccinia infections among them. It should be noted that Patient 1 was admitted to hospital May 3, and stayed until May 8; if infection of hospital personnel occurred during this time, the shortest interval between the time of infection and the time of collection of acute phase blood specimens was May 8 to June 10 (33 days). This interval is sufficient to produce a rise in antibody titers in a person in whom an asymptomatic vaccinia infection has developed. There is a report that serologic responses to smallpox antigens have been detected in asymptomatic contacts of overtly ill smallpox patients.[22] Since no isolation of virus was attempted in our study, it is possible that asymptomatic infection (for example, with pharyngeal excretion of virus) developed among one or more hospital personnel and accounts for spread of vaccinia virus from Patient 1 to Patient 2.

Pharyngeal excretion of vaccinia virus has been shown to occur in 18 of 80 vaccinated children.[23]

This was generally within the period of 6 to 12 days following vaccination, but as long as 20 days after vaccination in one case. Pharyngeal and urine viral cultures were negative for vaccinia virus in the study of Koplan and Marton[18] in each of eight volunteer vaccinees on days 2, 4, 7 and 10 postvaccination. Pharyngeal excretion of vaccinia virus has not been documented as a clinically significant means of vaccinia virus transmission.[23]

The structure of the double-doored isolation rooms with venting directly to the outside makes airborne spread of vaccinia virus unlikely in this hospital situation. However, airborne spread of smallpox infection within a hospital has been described.[24]

Two more plausible modes of transmission of vaccinia virus in this epidemiologic setting are by means of (1) either unrecognized fomites (such as creams, instruments, bed clothing) or other inanimate objects (such as walls) in the corridor of the ward where both patients were seen and (2) direct contact from first patient to hospital personnel to second patient. In the absence of clearcut information implicating the sharing of common body creams, instruments, bed linens, or other fomites, the most likely mode of transmission of vaccinia virus between these two patients is by direct contact from hospital personnel. However, it is also possible that Patient 2 became infected on May 8 by means of vaccinia virus on fomites in the hall visited by Patient 1 on the same day.

Recommendations for the Management of Patients with Vaccinia Virus Infection

From this experience with in-hospital transmission of vaccinia virus infection, several recommendations for the isolation and care of vaccinia patients may be formulated. (1) Hospital admission offices should consult the infection control nurse or hospital epidemiologist before admitting any patient with a diagnosis of vaccinia. (2) Patients with vaccinia virus infection should not be admitted to dermatology or other wards that contain high-risk patients, but should be managed either as outpatients, or admitted to a ward where minimum exposure to patients at risk can be assured. It is significant that several previously described nosocomial outbreaks of vaccinia virus infection occurred in dermatology wards.[4-6,8,9] (3) A patient isolated for vaccinia virus infection should be treated with vaccinia immune globulin (VIG) and discharged directly from the hospital. (4) Hospital personnel caring for patients with vaccinia virus infection should not work concomitantly with patients at high risk of acquiring vaccinia. (5) Hospital personnel should be alerted to the possibility of secondary cases of vaccinia virus infection, because the longer an undiagnosed patient remains unisolated, the greater the danger to other high-risk patients. (6) Recently vaccinated hospital personnel should be made aware that they are a potential hazard to high-risk patients because of the persistence of vaccinia virus at the vaccination site.[18]

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